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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,521	08/27/2001	Jianyun Dong	22488-710	7109

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/600,521	DONG ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47,58,59,67-69,71-73 and 115-119* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47, 58, 59, 67-69, 71-73 and 115-119* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Paper filed 1 August 2006 in response to the Final Office Action mailed 3 February 2006. Claims 47, 58, 59, 61, 67-69, 71-73 and 115-119 were considered in the 3 February Office Action. Claim 61 was canceled and claim 47 was amended in the 1 August Paper. Claims 47, 58, 59, 67-69, 71-73 and 115-119 are pending and under consideration.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1 August 2006 has been entered.

Response to Amendment and Arguments

35 USC §112 - Deposit Requirement

Claims 118 and 119 **stand rejected** under 35 U.S.C. §112, first paragraph, as lacking an enabling disclosure for the reasons of record and herein below in the response to arguments.

Response to Arguments

With respect to the Deposit Requirement, Applicant again asserts that the instant specification teaches the sequences for the structural elements that are to be mobilized into

intermediate vectors whose sequence maps are readily available. Thus, Applicant asserts one of skill will be able to construct the specific vectors of claims 118 and 119. (E.g., Remarks, p. 8, ¶¶ 1-2.) Applicant asserts that since the maps of the intermediate vectors are available and construction of vectors is routine in the art, one of ordinary skill in the art will be able to construct an adenoviral vector with the tet-responsive element and the transactivator element built into the opposite ends of the same vector.

This argument has been fully considered but is not deemed persuasive. It is again pointed out that each claim is directed to a specific vector, which is necessarily defined by a specific sequence of nuclei acids. That the maps of intermediate vectors are available is of little moment, because even a single nucleotide change (e.g., utilizing different restriction sites within the cloning site of an intermediate vector) would distinguish vectors that otherwise have the requisite structural elements (e.g., tet-responsive element, GFP, FasL).

Put another way, by claiming a specific vector, each claim is defined by a specific sequence for said vector. Therefore, a single unique sequence would correspond to the claimed vector in each of claims 118 and 119. Although the skilled artisan might be able to construct an adenoviral vector with the tet-responsive element and the transactivator element built into the opposite ends of the same vector, the skilled artisan would not know how to construct the vectors Ad_{TET} and Ad/FasL-GFP_{TET} (i.e., the claimed subject matter) because the skilled artisan does not know the precise sequence that defines the specifically claimed vectors. Therefore, in the absent of a biological deposit or a full sequence for the claimed vectors the skilled artisan would not know how to make what is claimed. Therefore, the claims stand rejected.

35 USC §112 - Enablement In Vivo

Claims 47, 58, 59, 67-69, 71-73 and 115-119 **stand rejected** under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing death in cancer cells in a solid tumor comprising transducing an adenoviral vector encoding a Fas ligand into cancer cells by injecting said adenoviral vector directly into said solid tumor mass, wherein expression of said Fas ligand is controlled by a tissue specific and an inducible promoter or an inducible promoter, does not reasonably provide enablement for a method as presently claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

This rejection is modified to acknowledge enabled scope beyond that indicated in the prior Office Actions but is maintained because the claims embrace subject matter that is not enabled by the specification for the reasons of record and herein below.

Response to Amendment and Arguments

At the outset, it is noted that the claims have been amended such that the method is now limited to injecting an adenoviral vector encoding a Fas ligand into cancer cells. As discussed herein below, the application does not teach inducing death in cancer cells by injecting an adenoviral vector directly into cancer cells, and given the wide distribution of cancer cells not limited to being comprised in a solid tumor, the skilled artisan would not know how to obtain a useful outcome *in vivo* by injecting an adenoviral vector encoding Fas ligand into cancer cells. That is because the skilled artisan would not how to locate cells of a disseminated cancer and

inject an adenoviral vector directly into a sufficient number of cells to obtain a useful outcome. If it is Applicant's intention that the claims actually read on a method wherein cells are transduced by injecting the vector into a tumor, the claims are enabled to the extent described herein above.

However, irrespective of what cancer cells are transduced, unpredictability is borne from systemic administration *and* immunotoxicity of utilizing adenoviral vectors in gene therapy. (E.g., Final Action, mailed 05/17/2005, p. 7, ¶¶ 2-3.) Therefore, within the context of systemic delivery of adenoviral vectors, the immunotoxicity is exclusive from the therapeutic being expressed. As repeatedly stated in previous Office Actions, the disclosure is not enabling for the claimed method to the extent it encompasses systemic administration. As noted in the Final Action, there is unpredictability with respect to practicing the invention *in vivo* with respect to vector neutralization via anti-adenoviral antibodies, and immunogenicity affecting transgene expression levels and viral vector distribution within the subject. For example, the duration of transgene expression can be reduced by the host's anti-virus immune response. In addition, as pointed out in previous Office Actions, in humans the adenoviral vector will rapidly localize to the liver upon systemic administration. Therefore, Applicant's assertion that a tissue-specific and an inducible promoter will limit expression to specific target cells is of little moment where the relevant art suggest that it is unpredictable whether the vector will be delivered to the target in the first place.

Applicant again contends that the example at p. 37, ll. 3-11 demonstrates that the virus could be administered without lethality and results in tumor cell growth retardation *in vivo*. However, as discussed in previous Office Actions, Applicant's examples are limited to expression of FasL in nude mice (immunocompromised). In addition, results in mice would not

necessarily translate to predictability for practicing the invention in larger mammals (e.g., human subjects). In any event, O'Connell teaches that there is a reasonable level of unpredictability in expressing a FasL *in vivo* insofar as any Fas^+ cell will interact with the ligand, whereby adverse effects include immune cell death or immunotoxicity.

In sum, neither the amendment nor Applicant's arguments are deemed sufficient to obviate the grounds of rejection of record and discussed in the foregoing. The rejections are maintained.

New Grounds

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47, 58, 59, 67-69, 71-73 and 115-119 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The MPEP states, "[i]f new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. §112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." (MPEP § 2163.06). The MPEP further states, "[w]henever the issue arises, the fundamental factual inquire is whether a claim defines an

invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in the application" (*Id.*, § 2163.02). The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

In the instant case, claim 47 has been amended such that it is directed to a method comprising "injecting an adenoviral vector encoding a Fas ligand into cancer cells that express a Fas receptor". In the remarks, p. 6, Applicant states that the amendment incorporates the limitation of claim 61. However, claim 47 was previously directed to a method comprising "transducing an adenoviral vector encoding a Fas ligand into cancer cells" and claim 61, which depended from claim 47 recited, "said cancer cells are transduced by direct injection of the adenoviral vector among cancer cells". (Emphasis added.) Thus, the previously examined claim 61 was directed to a method of transducing cancer cells by injecting the adenoviral vector into the vicinity of the cancer cells. In contrast, amended claim 47 requires injecting an adenoviral vector into cancer cells. The previous claim 61 does not support a claim wherein an adenoviral vector is injected into cancer cells, nor does the disclosure as originally filed. Therefore, the requirement that the vector be injected into cancer cells constitutes impermissible new matter.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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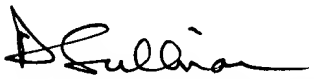

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636